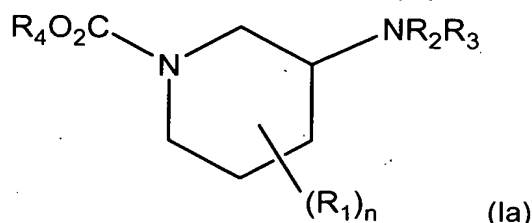
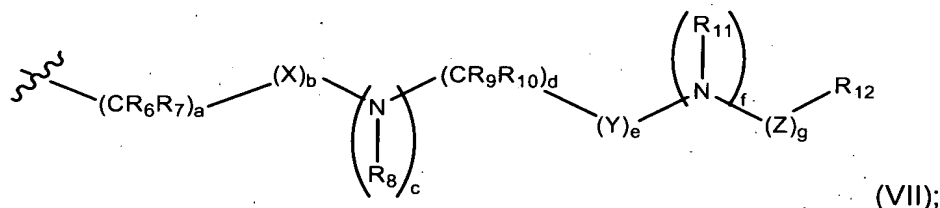


What is claimed is:

1. A method of making a compound of formula (Ia)



- 5 wherein R₁ is carboxy, cyano, deuterium, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)acyl, (C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH, (C₁-C₆)alkylamino-CO-, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)acyloxy(C₁-C₆)alkyl, nitro, cyano(C₁-C₆)alkyl, nitro(C₁-C₆)alkyl, trifluoromethyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)acylamino, (C₁-C₆)acylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)acylamino, amino(C₁-C₆)acyl, amino(C₁-C₆)acyl(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)acyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)acyl, R₁₅R₁₆N-CO-O-, R₁₅R₁₆N-CO-(C₁-C₆)alkyl, (C₁-C₆)alkyl-S(O)_m, R₁₅R₁₆NS(O)_m, R₁₅R₁₆NS(O)_m(C₁-C₆)alkyl, R₁₅S(O)_mR₁₆N, R₁₅S(O)_mR₁₆N(C₁-C₆)alkyl or a group of the formula (VII)
- 10
- 15



- 20 R₂ is hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, (C₂-C₆)alkenyl, or (C₂-C₆)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, trifluoromethyl, (C₁-C₄)alkoxy, (C₁-C₆)acyloxy, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, nitro, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl or (C₁-C₆)acylamino; or R₂ is (C₃-C₁₀)cycloalkyl wherein the cycloalkyl group is optionally substituted by deuterium, hydroxy, trifluoromethyl, (C₁-C₆)acyloxy, (C₁-C₆)acylamino, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, cyano(C₁-C₆)alkyl, trifluoromethyl(C₁-C₆)alkyl, nitro, nitro(C₁-C₆)alkyl or (C₁-C₆)acylamino;
- 25

R₃ is hydrogen, (C₁-C₆)alkyl, (C₃-C₁₀)cycloalkyl, (C₂-C₆)alkenyl, or (C₂-C₆)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted

by deuterium, hydroxy, halogen, trifluoromethyl, (C₁-C₄)alkoxy, (C₁-C₆)acyloxy, (C₁-C₆)alkylamino, (C₁-C₆)acylamino, ((C₁-C₆)alkyl)₂amino, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, cyano, cyano(C₁-C₆)alkyl, trifluoromethyl(C₁-C₆)alkyl, nitro, or nitro(C₁-C₆)alkyl ;

5 R₄ is (C₁-C₆)alkyl, (C₃-C₁₀)cycloalkyl, (C₂-C₆)alkenyl, or (C₂-C₆)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, halogen, amino, trifluoromethyl, (C₁-C₄)alkoxy, (C₁-C₆)acyloxy, (C₁-C₆)alkylamino, (C₁-C₆)acylamino, ((C₁-C₆)alkyl)₂amino, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, cyano, cyano(C₁-C₆)alkyl, trifluoromethyl(C₁-C₆)alkyl, nitro, or nitro(C₁-C₆)alkyl;
10

R₆, R₇, R₈, R₉, R₁₀ and R₁₁ are each independently hydrogen or (C₁-C₆)alkyl optionally substituted by deuterium, hydroxy, trifluoromethyl, (C₁-C₆)acyloxy, (C₁-C₆)acylamino, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, cyano, cyano(C₁-C₆)alkyl, trifluoromethyl(C₁-C₆)alkyl, nitro, nitro(C₁-C₆)alkyl or (C₁-C₆)acylamino; R₁₂ is
15 carboxy, cyano, amino, oxo, deuterium, hydroxy, trifluoromethyl, (C₁-C₆)alkyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)acyl, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂ amino, amino(C₁-C₆)alkyl, (C₁-C₆)alkoxy-CO-NH, (C₁-C₆)alkylamino-CO-, (C₂-C₆)alkenyl, (C₂-C₆) alkynyl, (C₁-C₆)alkylamino, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)acyloxy(C₁-C₆)alkyl, nitro, cyano(C₁-C₆)alkyl, nitro(C₁-C₆)alkyl, trifluoromethyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)acylamino, (C₁-C₆)acylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)acylamino, amino(C₁-C₆)acyl, amino(C₁-C₆)acyl(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)acyl, ((C₁-C₆)alkyl)₂amino(C₁-C₆)acyl, R₁₅R₁₆N-CO-O-, R₁₅R₁₆N-CO-(C₁-C₆)alkyl, R₁₅C(O)NH, R₁₅OC(O)NH, R₁₅NHC(O)NH, (C₁-C₆)alkyl-S(O)_m, (C₁-C₆)alkyl-S(O)_m-(C₁-C₆)alkyl, R₁₅R₁₆NS(O)_m,
20 R₁₅R₁₆NS(O)_m (C₁-C₆)alkyl, R₁₅S(O)_m R₁₆N, or R₁₅S(O)_mR₁₆N(C₁-C₆)alkyl;
25

R₁₅ and R₁₆ are each independently hydrogen or (C₁-C₆)alkyl;

X is S(O)_p, oxygen, carbonyl or -C(=N-cyano)-;

Y is S(O)_p or carbonyl;

Z is S(O)_p, carbonyl, C(O)O-, or C(O)NR-;

30 a is 0, 1, 2, 3 or 4;

b, c, e, f and g are each independently 0 or 1;

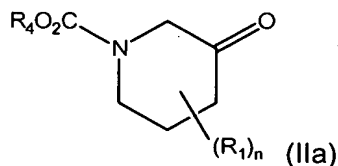
d is 0, 1, 2, or 3;

m is 0, 1 or 2;

n is 1, 2, 3, or 4;

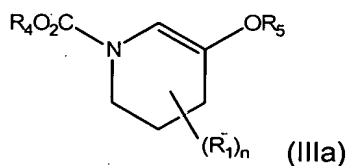
p is 0, 1 or 2; and

wherein the method comprises reacting NHR_2R_3 , $\text{N}(\text{CH}_3)\text{R}_2\text{H}$, or $\text{N}(\text{CH}_2\text{CH}_3)\text{R}_2\text{H}$ with a compound of formula (IIa)



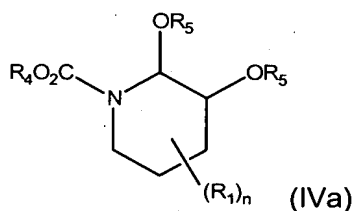
5 and reducing the compound so formed with a reducing agent.

2. The method of claim 1, wherein the method further comprises formation of the compound of the formula (IIa) by reacting a compound having the formula R_4OH , water, or R_4NH_2 and a compound of the formula (IIIa)



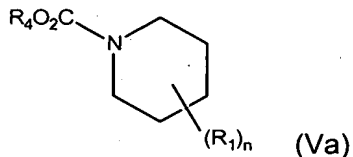
10 wherein R_5 is $\text{CO}(\text{C}_1\text{-C}_6)\text{alkyl}$.

3. The method of claim 2, wherein the method further comprises formation of the compound of the formula (IIIa) by heating a compound having the formula (IVa)



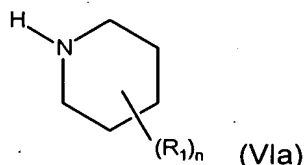
15 with a compound having the formula $(\text{C}_1\text{-C}_6)\text{alkyl}-(\text{C}=\text{O})-\text{O}-(\text{C}=\text{O})-(\text{C}_1\text{-C}_6)\text{alkyl}$.

4. The method of claim 3, wherein the method further comprises formation of the compound of the formula (IVa) by oxidizing a compound having the formula (Va)



20 under oxidizing conditions.

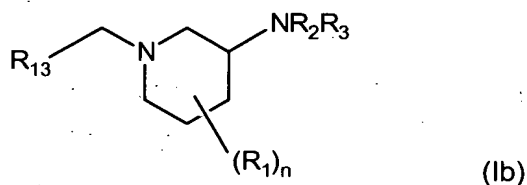
5. The method of claim 4, wherein the method further comprises formation of the compound of the formula (Va) by reacting a compound having the formula WCO_2R_4 and a compound having the formula (VIa)



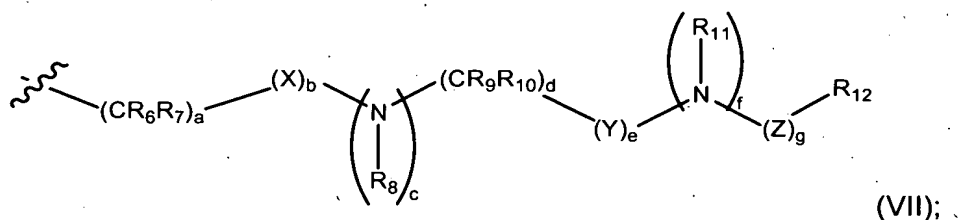
5 wherein W is halogen.

6. The method of claim 4, wherein the oxidizing conditions are an electrochemical oxidation.

10 7. A method of making a compound having the formula (Ib)



15 wherein R_1 is carboxy, amino, deuterium, hydroxy, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) alkylamino, amino (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_1-C_6) alkylamino, amino (C_1-C_6) alkyl, hydroxy (C_1-C_6) alkyl, (C_1-C_6) alkoxy (C_1-C_6) alkyl, nitro, nitro (C_1-C_6) alkyl, trifluoromethyl, trifluoromethyl (C_1-C_6) alkyl, (C_1-C_6) alkyl-S(O) $_m$, $R_{15}R_{16}NS(O)_m$, $R_{15}R_{16}NS(O)_m$ (C_1-C_6) alkyl, $R_{15}S(O)_m$ $R_{16}N$, $R_{15}S(O)_m$ $R_{16}N(C_1-C_6)$ alkyl or a group of the formula (VII)



20 R_2 is hydrogen, (C_1-C_6) alkyl, (C_1-C_6) alkylsulfonyl, (C_2-C_6) alkenyl, or (C_2-C_6) alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C_1-C_4) alkoxy, (C_1-C_6) alkylamino, $((C_1-C_6)alkyl)_2$ amino, nitro, (C_2-C_6) alkenyl, or (C_2-C_6) alkynyl; or R_2 is (C_3-C_{10}) cycloalkyl wherein the cycloalkyl group is optionally substituted by deuterium,

hydroxy, amino, trifluoromethyl, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, trifluoromethyl(C₁-C₆)alkyl, nitro, or nitro(C₁-C₆)alkyl;

R₃ is hydrogen, (C₁-C₆)alkyl, (C₃-C₁₀)cycloalkyl, (C₂-C₆)alkenyl, or (C₂-C₆)alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted
5 by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₄)alkoxy, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, trifluoromethyl(C₁-C₆)alkyl, nitro, or nitro(C₁-C₆)alkyl;

R₆, R₇, R₈, R₉, R₁₀ and R₁₁ are each independently hydrogen or (C₁-C₆)alkyl optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, trifluoromethyl(C₁-C₆)alkyl, nitro, or nitro(C₁-C₆)alkyl;
10 R₁₂ is carboxy, amino, deuterium, hydroxy, trifluoromethyl, (C₁-C₆)alkyl, trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂ amino, amino(C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkylamino, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, nitro, nitro(C₁-C₆)alkyl, trifluoromethyl,
15 trifluoromethyl(C₁-C₆)alkyl, (C₁-C₆)alkyl-S(O)_m, (C₁-C₆)alkyl-S(O)_m-(C₁-C₆)alkyl, R₁₅R₁₆NS(O)_m, R₁₅R₁₆NS(O)_m(C₁-C₆)alkyl, or R₁₅S(O)_mR₁₆N, or R₁₅S(O)_mR₁₆N(C₁-C₆)alkyl;

R₁₃ is (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₆-C₁₀)aryl, (C₁-C₆)carboalkoxy, (C₅-C₉)heteroaryl, (C₆-C₁₀)aryl(C₁-C₆)alkyl, or (C₅-C₉)heteroaryl(C₁-C₆)alkyl wherein the
20 R₁₃ group is optionally substituted by deuterium, hydroxy, amino, trifluoromethyl, (C₁-C₆)alkyl, (C₁-C₄)alkoxy, (C₁-C₆)alkylamino, ((C₁-C₆)alkyl)₂amino, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, trifluoromethyl(C₁-C₆)alkyl, nitro, or nitro(C₁-C₆)alkyl;

R₁₅ and R₁₆ are each independently hydrogen or (C₁-C₆)alkyl;

X is S(O)_p;

25 Y is S(O)_p;

Z is S(O)_p;

a is 0, 1, 2, 3 or 4;

b, c, e, f and g are each independently 0 or 1;

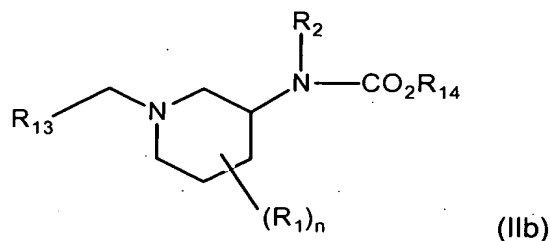
d is 0, 1, 2, or 3;

30 m is 0, 1 or 2;

n is 1, 2, 3, or 4;

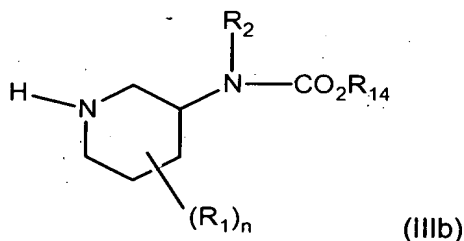
p is 0, 1 or 2; and

wherein the method comprises reducing a compound of formula (IIb).



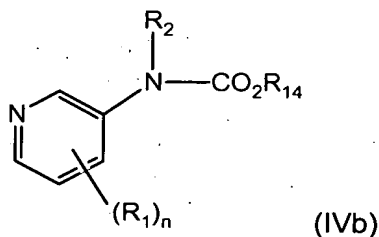
with a reducing agent, wherein R_{14} is (C_1-C_6) alkyl, (C_3-C_{10}) cycloalkyl, (C_2-C_6) alkenyl, or (C_2-C_6) alkynyl wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by deuterium, hydroxy, halogen, amino, trifluoromethyl, (C_1-C_4) alkoxy, (C_1-C_6) alkylamino, $((C_1-C_6)$ alkyl)₂amino, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, trifluoromethyl (C_1-C_6) alkyl, nitro, or nitro (C_1-C_6) alkyl.

8. The method of claim 7, wherein the method further comprises formation of the compound of the formula (IIb) by reacting a compound having the formula (IIIb)



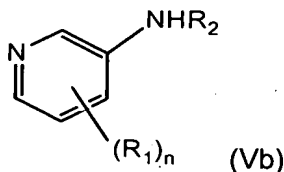
with an aldehyde of formula $R_{13}-(C=O)-H$ and reducing the compound so formed with a reducing agent.

9. The method of claim 8, wherein the method further comprises formation of the compound of the formula (IIIb) by hydrogenating a compound having the formula (IVb)



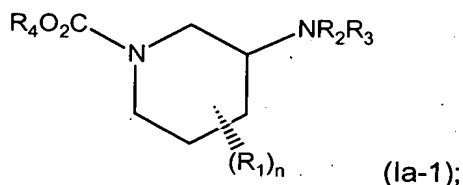
in the presence of a catalyst.

10. The method of claim 9, wherein the method further comprises formation of the compound of the formula (IVb) by reacting a compound having the formula (Vb)



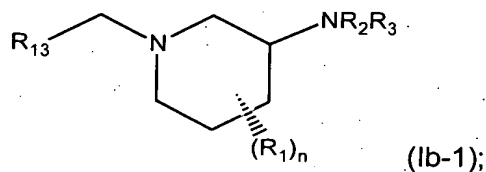
with $(R_{14}-O-(C=O))_2O$ or $R_{14}-O-(C=O)-X$ wherein X is halo.

11. The method of claim 1, wherein the compound of formula (Ia) has the relative stereochemistry of formula (Ia-1)



R_1 is (C_1-C_6) alkyl; n is one; R_2 and R_3 are each hydrogen or (C_1-C_6) alkyl; and R_4 is (C_1-C_6) alkyl.

12. The method of claim 7, wherein the compound of formula (Ib) has the relative stereochemistry of formula (Ib-1)



R_1 is (C_1-C_6) alkyl; n is one; R_2 and R_3 are each hydrogen or (C_1-C_6) alkyl; and R_{13} is (C_6-C_{10}) aryl.

13. The method of claim 1, wherein the reducing agent is a borohydride.

14. The method of claim 7, wherein the reducing agent is lithium aluminum hydride.

15. The method of claim 9, wherein the catalyst is Rh/alumina or Rh/C.